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Good Clinical Practice in Developing Countries: Applying Recommendations

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Abstract – The recommendations for clinical research in developing countries were published in 2007 and the present article deals with issues which were not initially raised or discussed in depth. In particular, we discuss specific questions linked to trials conducted in developing countries with regard to informed consent, research project review by two ethics committees, standards of care, management of biological samples, study follow-up committees, notification of Serious Adverse Events, paediatric trials, and Contract Research Organizations.

This article follows an initial publication in Thérapie[1] on the subject of clinical research in developing countries. The latter publication raised the following questions: 1) the parallel review of projects by ethics committees in the "Northern" country sponsoring the study and in the "Southern" country where the research is to be conducted, 2) the role of the independent committee in the monitoring of the study, 3) the notification of serious adverse events, and 4) post-trial commitments. The present article summarizes the development of certain themes that were not initially discussed in depth. Our objective is to propose for each of these themes concrete recommendations for guaranteeing both the scientific validity of trials conducted in developing countries and the respect of universal ethical rules. The general framework of discussions was that of clinical trials carried out by a sponsor from a ("Northern") industrialised country in a ("Southern") developing country.

1. Introduction

Scientific and ethical requirements for the conduct of clinical trials are identical throughout the world and established by international guidelines, and primarily the Good Clinical Practice guidelines.[2] Within this fundamental framework, it is sometimes necessary to adapt practices in order to respond to needs and realities in developing countries. For the clinician or the investigator, populations called upon in developing countries often correspond to the definition of "vulnerable populations" as defined by the Recommendations of the Council for International Organizations of Medical Sciences (CIOMS).[3]

2. Parallel ethics reviews

The 2006 Giens Round Table recommended that France adopt international recommendations[3] requiring that projects conducted in the South by sponsors from the North be reviewed by two ethics committees: a local committee (where the study is to be carried out) and a committee in the country of the sponsoring organization in the North. In 2007, despite the positions taken by the National Consultative Ethics Committee (Comité Consultatif National d'Ethique),[4,5] French legislation – dedicated to protect individuals taking part in trials in France – did not foresee that Committees for the Protection of Individuals (Comités de Protection

⋆ For a list of participants, see the end of the article.

des Personnes) pronounce themselves on trials conducted outside of France.

The 2007 Round Table confirmed the importance of presenting protocols to two committees so as to review the project independently albeit in a complementary fashion. If materially possible, it was deemed advisable that the sponsor first obtain the opinion of the Northern Committee, in order to be sure that the rules of their own country are respected before submitting it to the Southern Committee. A modification of the European Directive on Clinical Trials[6] could provide an opportunity for introducing throughout the EU the notion of parallel ethics reviews, while leaving each country free to decide on the specific modalities of its application. In France, the composition and functioning of the existing Committees for the Protection of Individuals would allow them to give consultative opinions on projects conducted in the South without increasing the complexity of existing systems.

3. Informed consent

Free and informed consent of individuals participating in trials is one of the fundamental cornerstones of ethics in clinical research. The principle of individual consent devoid of constraint and underpinned by clear and correctly documented information applies both to developing and industrialised countries.[1] In the North as in the South, problems arise regarding the pertinence of information given to patients. When considering the particular context of developing countries, a certain number of texts provide recommendations concerning informed consent such as the UNESCO (United Nations Educationnal, Scientific and Cultural Organisation) Universal Declaration[7] on Bioethics and Human Rights and the WHO-TDR Recommendations (World Health Organisation - Special Programme for Research and Training in Tropical Diseases).[8] Needless to say, large differences can exist depending on country and culture, on whether trials are to be conducted in urban or rural settings, etc. It should be further stressed that in developing countries the patient is usually expected to pay direct health care costs. Thus from the patient's point of view, inclusion in a clinical trial may represent (or be perceived as) the sole option for having access to appropriate care. Freedom of consent must thus be considered in the light of this fact.

The Round Table felt that it was fundamental that the conditions in which the consent of patients in developing countries was obtained be precisely documented and where necessary reconstituted in hindsight. In order to do so, it was recommended that the study protocol specify as minutely as possible the way the consent is to be solicited and obtained given the particular local context of each study. In the North, a "standard" paragraph of the protocol concerning information and acquisition of consent may be acceptable, because the principles and modalities thereof entered into common practice many years go and the fundamental principles are coherent with Western culture. However, we believe that a standard paragraph is insufficient for developing countries because it does not take into account the reality of the process set up for informing patients and gathering their consent. For instance it will be important to specify in the protocol which languages will be used for written documents and oral explanations, how illiterate persons will be informed and their consent obtained, how possible witnesses will be chosen and classified, whether an action of community information will be organised, whether methods will be applied to evaluate acceptance, how children's consent will be obtained, etc. This information in addition to precise written documentation will allow study monitors to have a clearer idea of the authenticity of informed consent and respond to possible queries after the trial. With regard to informed consent, a parallel North-South ethics review is particularly important in order to avoid "double standard". In case of persisting disagreement between committees, the opinion of the Southern Committee shall prevail.

4. Standard of care

At the end of 1990s a controversy arose over the notion of standard of care regarding the use of placebo in trials of antiretroviral drugs for preventing mother-to-child transmission of HIV in Africa.[9] The efficacy of these treatments had been demonstrated in the North, but the duration and complexity of treatment as well as the anticipated costs linked to care made the use of such drugs highly complex if not impossible in the South. Certain scientists had deemed it necessary to compare a short oral treatment with a placebo. The question was then raised as to whether the standard of care applied to patients in a research setting should be the best available standard worldwide or locally. The Helsinki Declaration was revised in 2000 and stated that the comparison of a new method must be conducted using "the best current prophylactic, diagnostic, and therapeutic methods".[10] This revision gave rise to many publications in which the supporters of a single universal standard opposed to the notion of "double standard" argued with those who contested such an approach in the name of feasibility of trials and their pertinence in the case of poor populations in developing countries who would not in any case have access to such standards. By 2002, the Nuffield Council of Bioethics in the United Kingdom had proposed a way of defining circumstances in which it was conceivable not to respect the "universal standard".[11]

The Round Table supported the approach proposed by Wendel *et al.* of the National Institutes of Health (NIH) Bioethics Center[12] according to which the best available standard should

be used while accepting exceptions to the rule on four conditions: one, there must be a scientific justification for using a "local standard"; two, the question posed must be pertinent for the local population; three, the community must be expected to obtain sufficient benefit and, lastly, the risk-benefit must be acceptable for subjects participating in the study. The Round Table wished to see a fifth condition added, namely the methodology used must have been demonstrated to provide scientific answers to the question posed. The limits of studies of non-inferiority in the case of comparison to "local standards" were stressed.[13–17] Indeed the demonstration of non-inferiority does not provide proof of true efficacy of an experimental treatment if the chosen comparator is not optimal. In the case of comparison with a "local standard", a trial seeking to demonstrate the superiority of the treatment under investigation rather than its equivalence might be preferred, especially if available data suggest that the local treatment does not have optimal efficacy. The ideal trial is to compare the treatment under investigation with both the "universal standard" and the "local standard". It is essential that when the rule of "universal standard" is not applied, this be done in total transparency in accordance with the ethics and regulatory authorities and that all decisions be clearly documented.

5. Management of biological samples

The issue of biological samples collected in the course of clinical investigations is complex and the same questions arise in the North and in the South regarding the property of these samples, their use to ends not initially foreseen, the patentability of certain discoveries, etc. The confidentiality of medical information as well as the patients' right to access information which concerns them and to give their opinion on its use must be respected. Developing countries may legitimately wish to acquire new techniques rather than let their samples go and be analysed abroad without any benefit for themselves. Following the 1992 declaration of the Convention of Biological Diversity, the so-called "Rio Convention",[18] more and more developing countries have become aware of the risk of having their samples kept in the North and used without their knowledge and possibly to mercantile ends. They have thus taken measures to oppose the exportation of such samples. In 2007, a controversy arose concerning the exportation of influenza virus strains in Indonesia[19] and the Russian customs service on its end temporarily blocked the exportation of biological samples as of May 2007. New recommendations have recently been adopted by OECD (Organisation of Economic Cooperative Development) countries concerning the management of biological samples.[20] These recommendations may provide appropriate means for the storage and quality management of biological samples collected in the South.

Recommendations of the Round Table

It is important to distinguish among three different types of situations: 1) collection of biological samples constituted for the sole purpose of research, 2) complementary analyses foreseen by the protocol but to be conducted after the actual research, and 3) changes in the final purpose of these complementary analyses *post-hoc*. The study protocol establishes the conditions in which the samples are conducted, preserved, and analysed. It may also include - along with the consent form - a clause regarding the possibility of conducting investigations complementary to those first foreseen if they are necessary for the pursuit of the initial study goal. In such conditions, the protocol must specify that the authorization of the ethics committee will be sought and, when materially possible, that patients will be informed. The situation is more complicated when investigators wish to use the samples for objectives entirely distinct from those initially foreseen by the study (change of final purpose). It does not seem possible to recommend a single attitude in such circumstances; thus, cases must be managed individually. Generally speaking, it is important that the decisions taken not endanger the rights and integrity of the patients nor the validity of collected samples and that of the trial, for example by accepting to compromise on the quality of conditions of preservation, transportation or analysis. When questions arise concerning the aftermath of a collection of samples preserved in the North, it may be appropriate to establish a "databank committee" composed of institutions both from the North and the South who will oversee the possible use of the samples stored in the North, perhaps many years later. Furthermore, in order to respond both to developing countries' wish to acquire new technologies and to that of guaranteeing the best possible quality of analyses, we recommend that samples be exported to a central laboratory in the North for the needs of the study, while helping the developing country to acquire expertise to be used afterwards. Finally, the group discussed the question of biological tests with possible consequences in terms of confidentiality and care of newly diagnosed patients, such as HIV or viral hepatitis tests. These questions can arise when one is seeking to ensure the protection of persons manipulating biological samples or in order to study concomitant disease. Whatever the motivations, the Round Table concluded that such tests could be conducted only when a) prior information of and consent from patients could be guaranteed and b) patient care by a national programme not solely dependent of the study sponsor is ensured.

6. Monitoring committees

The 2006 Round Table had recommended that clinical trials be monitored by two committees: 1) a Scientific Committee, *i.e.* a structure of the sponsor in charge of conceiving and coordinating

the study process and 2) an Independent Monitoring Committee (or Data and Safety Monitoring Board or Data Monitoring Committee, [DSMB or DMC]). The DSMB must be independent of the sponsor in order to safeguard the study. It is meant to avoid bias and methodological errors while contributing to the guarantee of patient safety. A DSMB is not required for all studies, but it is necessary when the treatments under investigation present potential risks in terms of tolerance or inefficacy, when the study concerns a serious disease lacking efficacious treatment, when it takes place in a context of intense activity of surrounding research and when it concerns vulnerable populations or individuals in emergency situations.

The present Round Table recommended that, for studies conducted in developing countries, the DSMB should include members representing the sponsoring country as well as the country in which the study is being conducted. It is important to ensure the independence of the DSMB members with regard to the sponsor and investigators and their autonomy with regard to local public health authorities. The DSMB's work relies on information gathered during the monitoring of the study and thus the quality of data is crucial if the DSMB is to fulfil its role. Finally, before beginning the study the practical rules and modalities for the functioning of the DSMB should be defined: transmission of data, organization of meetings, documentation of decisions, "confidentiality" with regard to investigators and promoter, etc. This is nevertheless often rendered complex owing to material conditions in developing countries.

7. Notification of Serious Adverse Events (SAE)

The recommendations of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[21] require the sponsor to inform the health authorities of SAE occurring during clinical trials within a period of 8 to 15 days depending on whether the SAE implicates or not vital prognosis, as well as to provide an annual report on the tolerance to the drug under study. The investigators dealing with the drug under study must also be informed of the occurrence of SAE declared in other investigation centres. The 2006 Round Table recognized the difficulty of fulfilling these obligations because SAE registration and treatment structures are often lacking in developing countries.

The present Round Table recommended that setting up clinical trials in developing countries provide an opportunity for consulting with local authorities on the information network to be established for SAE. It is important to collaborate with local authorities before the onset of the study in order to ensure that they are prepared to receive and manage SAE notifications. In addition to those documents required by the regulations, it may be appropriate to provide summary documents more easily used by the authorities, such as an annual report on the progress of the study which would summarize the conclusions of the DSMB reports. Likewise, the way of informing investigators should be considered case by case, respecting local and international legal frameworks in order to provide the most appropriate information possible. The Round Table stressed the importance that each study engages in awareness activities and transmission of expertise in drug safety monitoring to developing country authorities and investigators.

8. Paediatric trials

In the North as in the South, clinical research in paediatrics raises particular methodological and ethical problems, and identical (or equivalent) standards must be applied. These questions are particularly relevant in the South because the vast majority of clinical trials in infectious diseases conducted in developing countries involve children. Infectious diseases, essentially tuberculosis, diarrhoeas, malaria, measles, and HIV/AIDS, cause more than half of premature deaths, usually in children and young adults.[22] Specifically, problems in the developing world are largely linked to the economic and social context of many countries which usually limits the access of children to treatment. In addition, cultural factors sometimes have consequences on the perception of the importance of child health or notions that are in contradiction with the Western culture of the child as "king". Certain children are particularly vulnerable, such as street children or those totally marginalized by society or else those living in countries where access to treatment is possible only through school attendance. Exemptions when conducting trials in vulnerable populations, for example in the case of emergency situations or major direct benefit, are justified in very particular situations. Discussions around this topic did not lead to total consensus among participants. However, all agreed on the importance of stressing that even in situations of great impoverishment, the clinical trial cannot provide an alternative to treatment in face of lack of access to care.

9. Contract Research Organizations

Contract Research Organizations (CRO) are increasingly active in developing countries. The term CRO includes companies or organizations involved in various activities, under the responsibility of the trial sponsor or the organization in charge of drug development. They help meet rising needs in terms of recruitment of patients required by regulation authorities and by the tendency of many industrial sponsors to externalize clinical research activities. In addition, they respond to opportunities offered by large emerging countries and their diversity allows them to adapt to the laws of supply and demand. Their contribution may be limited to technical

advice, data analysis, drafting of documents, conduct of clinical trials, but they may also be asked to manage important parts of the clinical development of new drugs. Certain CROs employ several tens of thousands of collaborators throughout the world, whereas others are implanted in only one country and commission relatively few people. In developing countries, most CROs use local subcontractors for all or part of their activities. Certain large CROs have passed agreements with young companies ("start-ups") in order to lead the development of drugs from phase I all the way to registration. In certain cases, such conditions may result in CROs taking on the role of sponsor and the ensuing responsibilities. Indeed, in developing countries, one may question the role of CROs if their involvement leads to situations of *de facto* monopolies given their implantation in the country, their capacity to recruit, the development of data management tools which then become "indispensable" and disproportional with regard to the trial. The situation of CROs is evolving very rapidly and it has not been possible to investigate the situation fully. In 2003, their worldwide involvement concerned 64% of clinical trials from phase I to III, whereas ten years earlier (1993) it had been only 28%.[23] It appeared of great importance to the Round Table that when trials are conducted in developing countries together with CROs, a detailed document be drawn up listing all involved partners, including possible subcontractors, and specify the roles and responsibilities of all those concerned in both legal and operational terms.

10. Conclusion

The work conducted during the 2006 and 2007 meetings at Giens on clinical trials in developing countries showed that the fundamental principles of scientific validity and respect for ethics demand identical standards in the North and in the South. The recommendations issued on particular points are in agreement with the threefold concern: 1) to respect the specificities of developing countries, 2) not to impose upon them heavy and unjustified constraints that might result in penalization, but also 3) not to accept compromises on essential questions, in particular as regards vulnerable populations. We realized the difficulty of formulating general recommendations on the basis of inevitably limited experience, while avoiding excessive simplification and the risk of distortion of reality. Developing countries represent an infinite variety of situations in constant evolution. Many of today's rules of conduct and requirement measures will perhaps be outdated very soon. However, it can be reasonably stated that questions arising during clinical trials can be resolved – while respecting current regulations – by associating all stakeholders in decision-making and working in total transparency, both in the South and in the North.

Participants

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